CLINICAL PROBLEM-SOLVING

The Right Angle

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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A 25-year-old man presented to a local emergency department with abdominal distention and discomfort. He had first noticed an increased abdominal girth 12 months earlier and attributed it to excessive beer intake, but it progressed after he cut back on alcohol. His abdominal distention was associated with early satiety, fatigue, and exertional dyspnea.

The isolated symptom of abdominal distention is frequently explained by functional gastrointestinal disorders such as the irritable bowel syndrome, but when it is accompanied by early satiety, fatigue, and dyspnea, more serious conditions such as ascites, gastrointestinal hypomotility or obstruction, or an intraabdominal mass should be considered. Abdominal discomfort also may be a manifestation of celiac sprue or inflammatory bowel disease, particularly in a young man, or it may indicate a condition related to alcohol intake such as gastritis, hepatitis, or pancreatitis. Early satiety suggests impairment of gastric filling from a mass or an enlarged adjacent organ or impaired motility. Dyspnea could be accounted for by anemia from a gastrointestinal disorder or by right heart failure or constrictive pericarditis with hepatic congestion and ascites. Ascites with intraabdominal distention may itself cause dyspnea due to reduced lung volume.

The patient had a history of depression. He also reported a history of pneumonia after spending spring break in Florida 2 years previously, and he was told at that time that he had "fluid" around his lung and heart. His only medications were citalopram and as-needed clonazepam. He chewed tobacco and for several years drank 6 beers per day with weekly binges of up to 12 beers at a time. He had never received a blood transfusion or a tattoo, and he had no history of intravenous drug use. His family history was unremarkable.

On physical examination, the patient appeared to be in mild discomfort. He was afebrile, with a blood pressure of 137/87 mm Hg, a pulse of 67 beats per minute, a respiratory rate of 14 breaths per minute, and an oxygen saturation of 99% while he was breathing ambient air. There was no evidence of a jugular venous pulse with the head of the bed elevated to 30 degrees. His chest was clear on auscultation, and the heart sounds were regular, with no murmur, rub, or gallop. His abdomen was tense, with shifting dullness and mild, diffuse tenderness. The skin examination did not reveal jaundice, caput medusae, or telangiectasias. His legs were warm, without edema. The remainder of the examination was normal.

Ascites is strongly suggested by the tense abdominal distention and shifting dullness, but cutaneous manifestations of cirrhosis are absent. The history of simultaneous pleural and pericardial effusion raises the possibility of a diffuse serosal inflammatory process (e.g., systemic lupus erythematosus or tuberculosis) that initially mimicked pneumonia and now involves the peritoneum. Although the family history is unremarkable, inherited liver diseases such as hemochromatosis or Wilson's disease are possible. The normal jugular venous pressure and cardiac examination and the absence of edema do not provide support for a diagnosis of heart failure or constrictive pericarditis.

The white-cell count was 10,300 per cubic millimeter, the hemoglobin level 14.3 g per deciliter, and the platelet count 179,000 per cubic millimeter. The sodium level was 138 mmol per liter, potassium 4.2 mmol per liter, creatinine 0.9 mg per deciliter (80 μmol per liter), glucose 98 mg per deciliter (5.4 mmol per liter), aspartate aminotransferase 23 U per liter (normal range, 8 to 30), alanine aminotransferase 29 U per liter (normal range, 7 to 35), alkaline phosphatase 122 U per liter (normal range, 3 to 130), total bilirubin 2.1 mg per deciliter (35.9 μmol per liter) (normal range, 0.2 to 1.2 mg per deciliter [3.4 to 20.5 μmol per liter]), direct bilirubin 1.0 mg per deciliter (17.1 μmol per liter) (normal range, 0.0 to 0.3 mg per deciliter [0.0 to 5.1 μmol per liter]), total protein 7.3 g per deciliter (normal range, 6 to 8.3), albumin 4.1 g per deciliter, and lipase 14 U per deciliter. The prothrombin time was 12.7 seconds (international normalized ratio, 1.2), and the partial-thromboplastin time was 29.9 seconds.

An electrocardiogram showed sinus rhythm with right atrial enlargement (Fig. 1). An ultrasonographic examination of the abdomen showed marked ascites with splenomegaly and a mild increase in liver echodensity. Computed tomography (CT) of the abdomen and pelvis showed massive ascites and splenomegaly (Fig. 2).

The patient does not have the laboratory features of cirrhosis, with the exception of mild hyperbilirubinemia. The evidence of right atrial enlargement on electrocardiography suggests the possibility of right-sided heart failure, although the initial physical examination did not show peripheral edema or evidence of elevated jugular venous distention. The jugular venous pressure should be reassessed, since elevated pressure may become apparent only with different positioning of the patient. The spleen is enlarged, and the liver has mildly altered parenchyma detected on ultrasonographic examination. Decompensated alcoholic liver disease is unlikely, given the patient's young age and results of laboratory tests. Conditions resulting in infiltration of both the liver and spleen, such as lymphoma, tuberculosis, or sarcoidosis, should be considered.

Paracentesis was performed, and 3.5 liters of clear yellow fluid were aspirated. Testing of the fluid showed that the white-cell count was 245 cells per milliliter (32% neutrophils, 28% lymphocytes, 39% histiocytes, and 1% basophils) and the red-cell count was 1095 cells per milliliter. The albumin level was 2.5 g per deciliter (with a serum–ascites albumin gradient [SAAG] of 1.6 g per deciliter), total protein 4.7 g per deciliter, lactate dehydrogenase 106 U per liter, amylase 18 U per liter, and triglycerides 56 mg per deciliter (0.6 mmol per liter). Gram's staining was negative. Bacterial and fungal cultures showed no growth. Staining for acid-fast bacilli was negative; the results of a mycobacterial culture were pending. Cytologic analysis of the fluid and of a cell block showed no malignant cells.

The elevated SAAG (>1.1 g per deciliter) points to portal hypertension as the cause of the patient's ascites. Cirrhosis, heart failure, and the Budd–Chiari syndrome are thus more likely than peritoneal carcinomatosis and tuberculosis, which are associated with a low SAAG. The low absolute neutrophil count and the results of staining and cultures also argue against infection, and the results of cytologic analysis of the peritoneal fluid and the available clinical data do not suggest a malignant condition. Patients with cardiac ascites may have an elevated SAAG, an elevated protein level in peritoneal fluid, and relatively normal liver biochemical values. Echocardiography will be helpful in assessing right ventricular function, the pericardium, and pulmonary-artery pressures.

Testing was negative for hepatitis B surface antigen and core and surface antibodies, hepatitis C virus (on polymerase-chain-reaction assay), human immunodeficiency virus antibodies, and an-

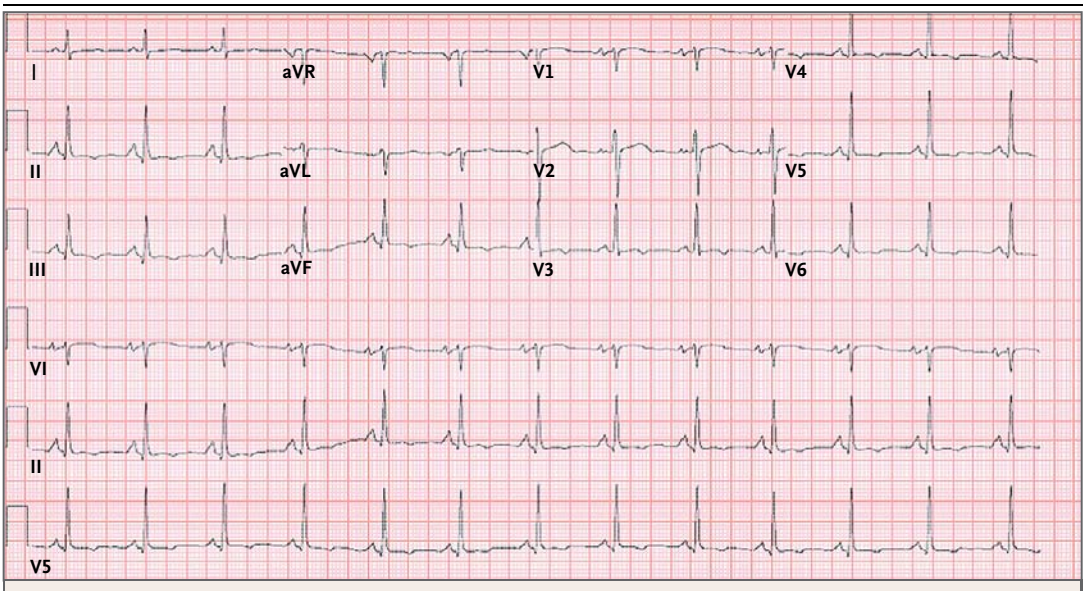

Figure 1. Electrocardiogram Showing Normal Sinus Rhythm and Right Atrial Enlargement.

tinuclear antibodies (ANA). The level of alpha$_1$-antitrypsin was 224 mg per deciliter (normal range, 113 to 263), the serum ferritin level 602 ng per milliliter, the transferrin saturation 13%, the ceruloplasmin level 33 mg per deciliter (normal range, 16 to 36), the B-type natriuretic peptide (BNP) level 101 pg per milliliter (normal value, <100), and the alpha-fetoprotein level 3.2 ng per milliliter (normal value, <7.9). A 24-hour urinary copper level was 24 μg per total volume (normal value, <55). Dedicated magnetic resonance imaging (MRI) of the liver showed mild, nonspecific parenchymal lobulation, with no portal or hepatic-vein thrombosis.

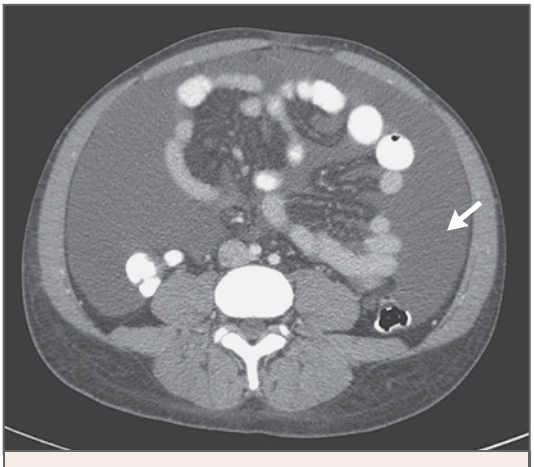

Figure 2. CT Scan of the Abdomen, Showing Massive Ascites (Arrow).

Laboratory testing for various causes of chronic liver disease is unrevealing. The absence of vascular obstruction is informative. Attention to other posthepatic causes of ascites is warranted. The low BNP level argues against biventricular or left-sided heart failure, but it may occur in constrictive pericarditis.

Transjugular liver biopsy showed pericellular fibrosis with sinusoidal dilatation consistent with chronic venous outflow obstruction, but no cirrhosis (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Transjugular liver manometry revealed elevated right atrial venous pressure (32 mm Hg) and hepatic venous pressure (30 mm Hg), with no portosystemic gradient (hepatic-vein wedge pressure, 32 mm Hg).

Transthoracic echocardiography was technically difficult to perform, but it suggested normal left ventricular size and function, no valvular disease, and mild right atrial and ventricular enlargement. An abnormal "bounce" of the interventricular septum was noted (Video 1, available at NEJM.org). The estimated right ventricular systolic pressure was 20 mm Hg on the basis of an estimated right atrial pressure of 5 mm Hg.

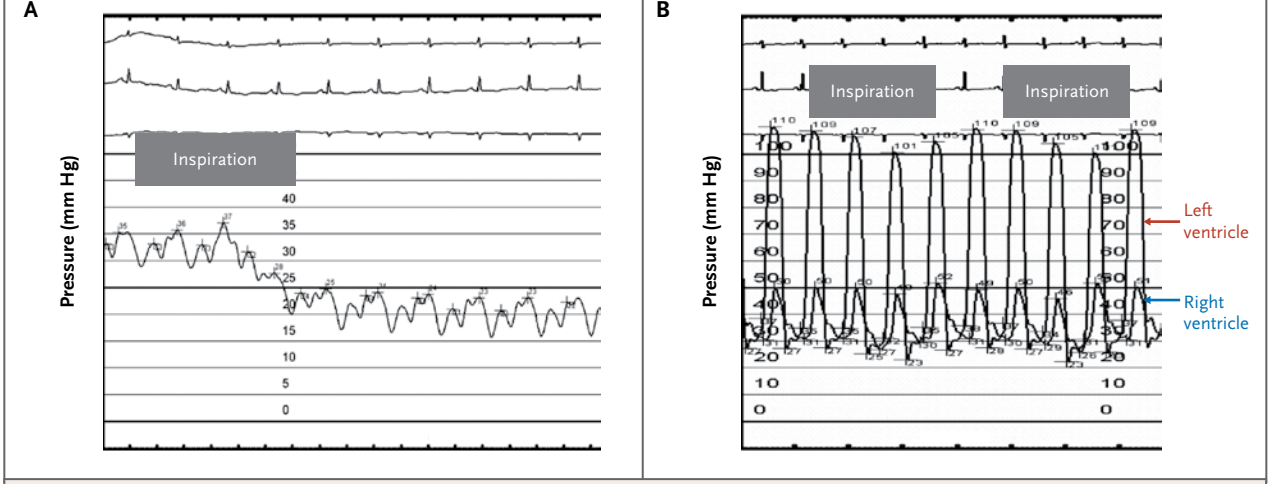

Figure 3. Right Heart Catheterization.

Hemodynamic tracings show increased superior vena caval pressure with inspiration (Kussmaul's sign) (Panel A) and ventricular dip and plateau (the "square root sign"), as well as ventricular interdependence (Panel B).

Two important findings are the absence of a portosystemic gradient, which rules out portal hypertension of hepatic origin, and evidence of elevated right-sided cardiac pressures. On the basis of the measured right atrial pressure of 32 mm Hg, the actual right ventricular systolic pressure is nearly 50 mm Hg. The liver histologic findings suggest chronic congestion.

The major differential diagnosis at this point is pulmonary hypertension versus constrictive pericarditis leading to hepatic congestion; restrictive cardiomyopathy is also a consideration. The interventricular septal bounce may reflect right ventricular pressure overload or interdependence between the right and left heart chambers; this is common in constrictive pericarditis. Dedicated tissue Doppler echocardiography is useful in distinguishing constrictive pericarditis from restrictive cardiomyopathy. There is no evidence of pericardial thickening on echocardiography, but MRI or CT is more sensitive. Characteristic hemodynamics can be seen on right heart catheterization.

Right and left heart catheterization revealed elevation and equalization of right atrial pressure (29 mm Hg), pulmonary capillary wedge pressure (30 mm Hg), pulmonary arterial pressure (45/30 mm Hg; mean, 36 mm Hg), right ventricular diastolic pressure (30 mm Hg), and left ventricular diastolic pressure (30 mm Hg). The cardiac index was markedly reduced (1.68 liters per minute per square meter of body-surface area as measured by thermodilution and 1.87 liters per minute per square meter as measured by the Fick method). Tracings from the right heart catheterization showed an inspiratory increase in superior vena caval pressure (Kussmaul's sign) (Fig. 3A). A dip and plateau (the "square root sign") of the right ventricular pressure and interdependence of the right and left ventricles were also evident (Fig. 3B). Coronary angiography was normal. CT of the thorax showed small, nonspecific mediastinal and left axillary lymphadenopathy (which was thought to be reactive) but no pericardial thickening. Cardiac MRI showed biatrial enlargement, a dilated inferior vena cava and hepatic vein, a ventricular septal bounce, and mild pericardial thickening (Fig. 4 and Video 2).

Videos of transthoracic echocardiographic and cardiac MRI studies are available at NEJM.org

The hemodynamic and imaging findings are all consistent with constrictive pericarditis. Although the jugular venous pressure was not reported to be elevated on physical examination, this may have been because the height of the column was too great or because this finding, which can be challenging to assess, was assessed inaccurately.

Most cases of constrictive pericarditis are idiopathic, but the pleural and pericardial illness 2 years previously, the mediastinal and left axillary lymphadenopathy, and the small pulmonary

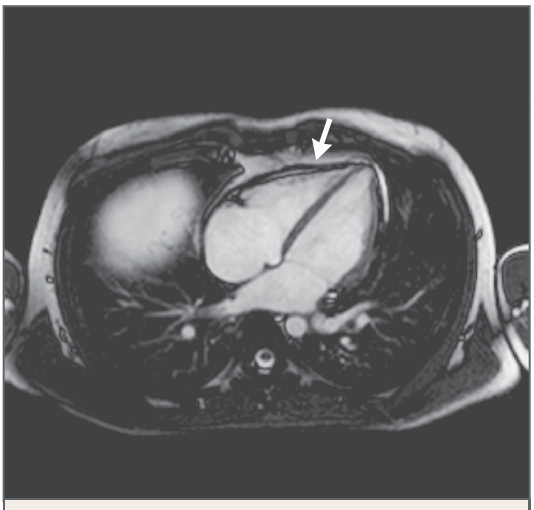

Figure 4. MRI Scan of the Heart.
Biatrial enlargement and mild pericardial thickening (arrow) are evident.

nodules suggest the possibility of a systemic disease. Given the absence of other features consistent with systemic lupus erythematosus and the negative ANA test, I think that diagnosis is unlikely. Acute tuberculosis could have been the cause of the patient's previously reported pneumonia. Sarcoidosis can be mistaken for pneumonia, although diffuse serosal involvement is uncommon. Lymphoma must also be considered but would be unlikely to explain an illness from 2 years earlier. Histologic analysis and culture of a surgical specimen should be performed after therapeutic pericardiectomy, but even with these assessments, a cause is not identified in up to 50% of cases of constrictive pericarditis.

The patient was referred for pericardiectomy. Dissection and removal of the fibrosed and adherent anterior pericardium from the left to the right phrenic nerve resulted in almost immediate normalization of filling pressures and cardiac output (Fig. 5A). Pathological examination of the pericardium showed fibrosing pericarditis with no granulomas (Fig. 5B). Gram's staining, staining for acid-fast bacilli, and cultures of the pericardium for bacteria, fungus, and acid-fast bacilli were negative.

Seven months after the operation, the patient reported a 30-lb (13.6-kg) weight loss, dramatic improvement in his exercise tolerance, and no abdominal swelling.

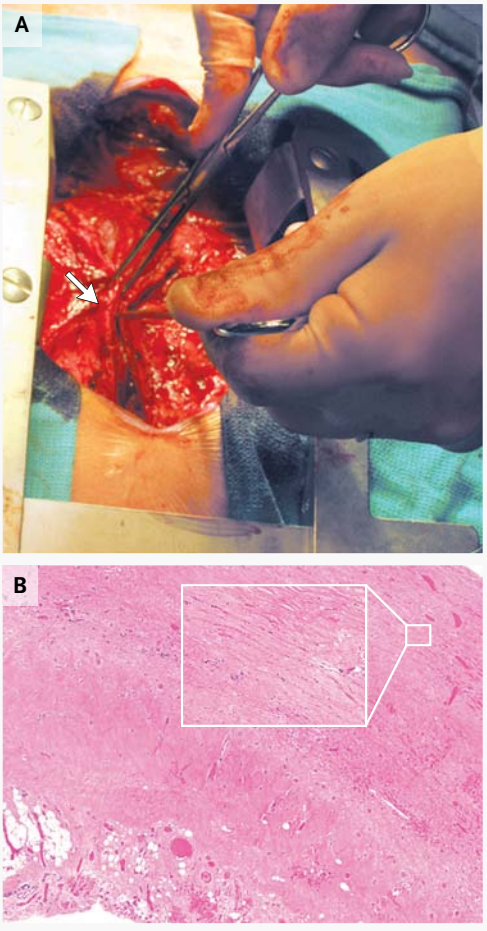

Figure 5. Surgical and Pathological Findings.
Panel A shows a gross photograph of thickened and fibrosed pericardium (arrow) in the operating room. Panel B shows hematoxylin and eosin staining of a pericardial specimen, revealing paucicellular fibrosis and hemosiderin-laden macrophages (inset) suggestive of previous injury.

COMMENTARY

This case illustrates an unusual cause of ascites in a young man. The most common cause of ascites in the United States is cirrhosis, followed distantly by cancer, right-sided heart failure, tuberculosis, pancreatic disease, and various rare infectious and hematologic diseases.[1] Since cirrhosis is less common in younger patients than in older patients, consideration of other potential causes was particularly warranted in this case. When ascites is present, estimation of the jugular venous pressure is critical, since it can fre-

quently separate cardiac from noncardiac causes. In this case, the failure to recognize the elevated jugular venous pressure led to a delay in diagnosis and extensive diagnostic testing.

Elevated jugular venous pressure can be challenging to detect, even when the assessment is made by experienced clinicians. The overall correlation between clinical assessment of the jugular venous pressure and direct measurement of central venous pressure by central venous catheterization is poor; an overall accuracy of 56% has been reported in classifying the central venous pressure as low, normal, or high, with a sensitivity for detection of a high central venous pressure (>10 cm of water) of less than 60%.[2-4] In this case, the failure to detect the high jugular venous pressure may have related at least in part to its extreme elevation. The jugular venous pressure is best estimated by identifying the right internal jugular venous pulse with the patient lying at 30 to 45 degrees and also sitting upright. When the jugular venous pressure exceeds 20 cm (equivalent to approximately 15 mm Hg), the pulse may not be visualized at all, since it would be above the angle of the jaw in most patients who are sitting upright.

In the present case, the discussant considered the correct diagnosis early and set it aside in light of the normal jugular venous pressure but returned to it once additional information was available. The elevated SAAG indicated portal hypertension, but a variety of laboratory tests excluded common causes of cirrhosis. Markedly elevated right atrial pressure and the absence of a portosystemic gradient on transjugular liver manometry pointed to right-sided heart failure as the source of portal hypertension. The equalization of diastolic pressures and ventricular interdependence on right and left heart catheterization confirmed constrictive pericarditis — a rare and elusive condition — as the source of the patient's right-sided heart failure and ascites.

Constrictive pericarditis is a consequence of inflammation, scarring, and fibrosis of the pericardium, resulting in an inelastic sac that impairs normal diastolic filling of the heart. Causes of constrictive pericarditis include previous cardiac surgery, radiation therapy, tuberculosis, trauma, cancers, and inflammatory diseases such as systemic lupus erythematosus or sarcoidosis; the majority of cases, however, are idiopathic.[5,6] Our patient's constrictive pericarditis may have resulted from his presumed viral infection 2 years previously. Symptoms of constrictive pericarditis are typically related to systemic venous congestion and low cardiac output. Whereas elevated jugular venous pressure was present in nearly all patients with constrictive pericarditis in a large case series, peripheral edema was absent in approximately 25% of patients, particularly early in the disease process, and less than 6% of patients presented with predominantly abdominal symptoms.[6]

Noninvasive testing can offer important clues to the diagnosis of constrictive pericarditis but may also be inconclusive. Pericardial thickening detected on CT or MRI is absent in up to 28% of patients with surgically proven constrictive pericarditis.[7] Typical echocardiographic findings, such as normal systolic function, a plethoric inferior vena cava, a restrictive mitral inflow pattern with respiratory variation (Fig. 2 in the Supplementary Appendix), reversal of expiratory hepatic-vein flow, a septal motion suggestive of enhanced ventricular interaction, or an elevated early diastolic mitral annular velocity (E′) detected by tissue Doppler imaging, may not be observed if images are poor or if constrictive pericarditis is not explicitly noted as a potential diagnosis.[8,9] Finally, because the myocardium is encased in a constrictive pericardial sac, BNP values are typically normal or only slightly elevated because of a lack of cardiac stretch.[10] A normal BNP level in this context may lead clinicians to incorrectly dismiss the possibility of a cardiac cause of ascites.

Elevated and equalized diastolic pressures on cardiac catheterization are the rule for constrictive pericarditis. Ventricular filling is rapid early and blunted late by the stiffened pericardial sac, leading to the characteristic steep y descent of right atrial pressure and the dip and plateau of ventricular pressure.[11,12] Although these hemodynamic patterns can be observed in other causes of heart failure such as restrictive cardiomyopathy, discordance between changes in right and left ventricular systolic pressures during respiration, known as ventricular interdependence, reliably distinguishes constrictive pericarditis from these other conditions.[13,14]

Most patients with constrictive pericarditis require surgical pericardiectomy. Removal of densely adherent pericardium is usually successful but can be extremely challenging.[6] Moreover, recovery can be delayed for several weeks, and patients in whom the constriction has progressed

to the point of abnormal ventricular function, severely reduced cardiac output, cachexia, or end-organ dysfunction derive the least benefit from the procedure,[5,15] an observation that underscores the importance of prompt diagnosis and treatment.

The diagnosis of constrictive pericarditis in our patient was probably delayed for two reasons: the rarity of the diagnosis and the failure to recognize the elevated jugular venous pressure on initial examination. This case reminds us that reconsideration of clinical information from a different angle can facilitate the diagnostic process in patients with complex conditions.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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